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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/045,721	10/26/2001	Naohiro Terada	5853-207	9675

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,721	TERADA ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendments and response filed 13 February 2004 has been received and entered.

Claim 7 has been cancelled.

Claims 1-6, and 8-20 are pending and considered.

Objections to the Claims

In light of Applicants amendments and arguments, the objections to Claims 5, 7, and 20 have been withdrawn.

Rejections under 35 USC § 102

In light of Applicants amendments and arguments, the rejection of Claims 1, 8-9 and 13-19 have been withdrawn. However, these rejections are moot in view of the new grounds of rejection below.

Rejections based on 35 USC 103

In light of Applicants amendments and arguments, the rejection of Claims 1, 8-9 and 13-19 have been withdrawn. However, these rejections are moot in view of the new grounds of rejection below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 14-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO 99/10535 to Liu, filed 21 August 1997, published 4 March 1999, of for reasons of record set forth in the

Claims 1 and 14-19 disclose methods to screen substances for the ability to promote cellular differentiation in stem cells in which cultured stem cells are contacted with a test substance, cultured, and tested for cellular markers of differentiation. The claims further require at least two separate cultures, each contacted with a different substance, and testing for increased tissue-specific gene expression as the cellular marker of differentiation. The depending claims limit the method of measuring expression of genes to measuring the cellular changes in mRNA expression, wherein such measuring can include isolation of total cellular RNA, cellular mRNA, reverse transcription to obtain cDNA, PCR amplification, immobilization of mRNA, and probing for specific mRNAs.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 obviates all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation … of stem cells" (Liu '535, ABSTRACT). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those

genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreoever, Liu '535 obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place. Liu '535 also teaches the aspects of mRNA isolation (p. 20), total cellular RNA isolation (p. 20), reverse transcription (p. 20), PCR amplification (pp. 23-24), immobilized mRNA (EXAMPLE 4), and probing for mRNA (EXAMPLE 4).

With regard to Claim 1, in view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify drug candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in the cultures for incrased tissue-specific gene expression markers. The Artisan would have been motivated to do so because Liu teaches that such screens would have use in many applications, including supportive care of cancer patients (p. 3, lines 28-30). Moreover, the Artisan would have had a

reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culture techniques for cells *in vitro* are routine.

With regard to Claims 14-19, in view of Liu, the artisan would have found it obvious to perform such methods and to analyze such expression by either isolating mRNA, total cellular RNA, reverse transcription of RNAs to create cDNAs, utilizing PCR to amplify and reverse transcribe such RNAs, immobilizing the RNAs on a substrate, and using probes that specifically hybridize to the RNAs of interest. The Artisan would have been motivated to do so in order to screen for the changes in gene expression as markers of differentation. Moreover, the Artisan would have had a reasonable expectation of success, because Liu had already shown such methods to work with hematopoietic stem cells.

Claims 1 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WIPO document No. WO 99/10535 to Liu, filed 21 August 1997, published 4 March 1999, as applied to claim 1 above, and further in view of U.S. Patent No. 5,328,844 to Moore, filed 24 June 1992, patented 12 July 1994.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 obviates all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535, ABSTRACT). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those

genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreoever, Liu '535 obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place.

With regard to Claim 1, in view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify druig candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in the cultures for incrased tissue-specific gene expression markers. The Artisan would have been motivated to do so because Liu teaches that such screens would have use in many applications, including supportive care of cancer patients (p. 3, lines 28-30). Moreover, the Artisan would have had a reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culture techniques for cells *in vitro* are routine.

However, Liu does not teach the aspects of culturing cells at about 37 degrees centigrade, incubating the cells in humidified and carbon-dioxide containing incubators, the use of microtiter plates, or the aspects of culturing for at least 5 or 7 days or 7-18 days.

On the other hand, Moore teaches culture media useful for establishing growing and maintaining mammalian cells in culture (ABSTRACT). More also teaches that cells are cultured in, *inter alia*, multi-well plates (microtiter plates), at 37 degrees centigrade, with 7.5% carbon dioxide, and may be cultured for 3, 7, 14 and 21 days (EXAMPLE 2).

In view of Liu and Moore, it would have been obvious to modify the teachings of Liu by culturing cells in microtiter plates, at 37 degrees centigrade, with 7.5% carbon dioxide, and for 3 to 21 days, as taught by Moore. The Artisan would have been motivated to do so in order to allow for such cells to differentiate and express the markers of differentiation, as differentiation takes time. Moreover, the Artisan would have had a reasonable expectation of success because Moore had shown that cells could be cultured for these time frames successfully.

Claims 1-5 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu as applied to claim 1 above, and further in view of U.S. Patent No. 5,874,301 to Keller, of record.

Claims 2-5 encompass the screen of Claim 1, and further limit the screen to (i) embryonic stem cells, (ii) mammalian embryonic stem cells, (iii) murine embryonic stem cells, and (iv) murine R1 cells. Claims 10-12 limit the time of culturing of the cells to less than 5, 7, or 7-18 days.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 obviates all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535, ABSTRACT). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreoever, Liu '535 obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place.

With regard to Claim 1, in view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify druig candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually,

under conditions that allow for such differentiation, and analyzing the cells in the cultures for incrased tissue-specific gene expression markers. The Artisan would have been motivated to do so because Liu teaches that such screens would have use in many applications, including supportive care of cancer patients (p. 3, lines 28-30). Moreover, the Artisan would have had a reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culture techniques for cells *in vitro* are routine.

Liu '535 does not teach these cell-type limitations, as it is directed to stem cells in general; however, Keller '301 teaches the isolation of embryonic cell populations (TITLE) and specifically teaches embryonic stem cells (col. 2, lines 5-8). Keller '301 also teaches mouse embryonic stem cells (Example 1). Mice are mammals, therefore, the limitation of mammalian embryonic stem cells is also taught. Keller '301 also teaches mouse embryonic stem cells in general (col. 2, lines 5-36), therefore one would have been motivated to use any mouse embryonic stem cell in practicing the invention, including mouse R1 embryonic stem cells. Lastly, Keller '301 teaches that preferred culture times are between 5 and 12 days (col. 9, lines 54-64).

Keller '301, is also a reference that the Artisan would have utilized to modify the teachings of Liu '535, and therefore obviates the above-listed claims. This is because Keller '301 specifically teaches that "[t]he cells are useful ... to identify compounds that control precursor cell growth and differentiation." Therefore, one of ordinary skill in the art would have modified Liu '535 to provide a method of screening compounds for cell growth and differentiation utilizing the embryonic stem cells as limited in the claims. Moreover, the artisan would have had a reasonable expectation of success, as Liu '535 teaches how to define the

system (ABSTRACT), and Keller '301 shows that these cells have been shown to undergo differentiation (col. 2, lines 5-33).

Claims 1and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of Thomson, et al. (1998) Science, 282:1145-1147, of record.

Claim 6 encompasses all the limitations of Claim 1, and further limits the cell type to human embryonic stem cells.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 obviates all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535, ABSTRACT). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreoever, Liu '535 obviates the limitation of culturing the cells after

contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place.

With regard to Claim 1, in view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify druig candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in the cultures for incrased tissue-specific gene expression markers. The Artisan would have been motivated to do so because Liu teaches that such screens would have use in many applications, including supportive care of cancer patients (p. 3, lines 28-30). Moreover, the Artisan would have had a reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culture techniques for cells *in vitro* are routine.

Liu '535 does not teach human embryonic stem cells; however, Thomson '98 teaches primate embryonic stem cells (TITLE), which includes the specific teaching of human embryonic stem cells (ABSTRACT).

Furthermore, one of ordinary skill in the art at the time of invention would have been motivated to modify the teachings of Liu '535 by the use of human embryonic stem cells as taught in Thomson '98, because Thomson '98 teaches that such embryonic stem cells are useful for drug discovery (ABSTRACT). Similar to the arguments for the combination of Keller '301 with Liu '535, the artisan at the time of the invention would have also had a reasonable

expectation of success because Thomson '98 demonstrates that these cells are capable of differentiation (p. 1146).

Claims 1 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu, as applied to claim 1 above, and further in view of U.S. Patent No. 5,143,854 to Pirrung, of record.

Although Liu '535 does not define the steps contemplated by Applicant in the same manner that Applicant defines these steps, Liu '535 obviates all of the limitations of the Applicant's claims. Specifically, Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535, ABSTRACT). Liu '535 teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (Id., p. 5, lines 1-6). This encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner, and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1. Furthermore, Liu '535 teaches a comparison of the gene expression profiles with that of a stem cell population treated with a substance, to identify substances that modulate the expression of these genes, and therefore would be associated with stem cell differentiation (Id., p. 5, lines 7-18, and EXAMPLES 2 and 3). Moreoever, Liu '535 obviates the limitation of culturing the cells after contacting the cells with the substance, as one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression to take place.

With regard to Claim 1, in view of Liu, one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would have been motivated to identify druig candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in the cultures for incrased tissue-specific gene expression markers. The Artisan would have been motivated to do so because Liu teaches that such screens would have use in many applications, including supportive care of cancer patients (p. 3, lines 28-30). Moreover, the Artisan would have had a reasonable expectation of success, as Liu had already shown that such screens could work *in vivo*, and culture techniques for cells *in vitro* are routine.

However Liu '535 does not teach the aspect of utilizing gene chip technology in the screening for tissue-specific gene expression.

On the other hand, Pirrung '854 teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung '854 teaches that such technology is useful for "[s]creening large numbers of polymers for biological activity," (col. 3, lines 39-41).

Moreover, one of ordinary skill in the art at the time of the invention would have been motivated to modify the teachings of Liu '535 by the gene chip technology of Pirrung '854 with a reasonable expectation of success because the gene chip technology of Pirrung '854 allows for the controlled synthesis of a variety of polymers in a small space (SUMMARY OF INVENTION), which is particularly suited to the screening system described. Also, because

both Liu '535 and Pirrung '854 have been shown successful, one would have expected success with their combination.

CONCLUSION

The objections to claims 5, 7 and 20 are withdrawn.

Claims 1-6 and 8-20 are rejected on new grounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER